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R₉ is selected from the group consisting of -C(O)-; and

B is -NH₂, -OH, Leu-Pro-NH₂, Leu-Hyp-NH₂,
Pen(CH₂COOH)-Pro-NH₂, Cys(CH₂COOH)-Pro-NH₂,
γ-carboxyglutamic acid-Pro-NH₂,
(N-carboxymethyl)Gly-Pro-NH₂,
(N-carboxyethyl)Gly-Pro-NH₂,
(N-1,3-dicarboxypropyl)Gly-Pro-NH₂,
(N-methyl)Leu-Pro-NH₂, Leu-NH₂, and Leu-OH.

21. (amended) A compound Ac-D-pAph-Chg-PalMe(3)-Leu-Pro-NH₂.

22. (amended) A compound Ac-D-pAph-Chg-PalMe(3)-NH₂.

REMARKS

Claims 2, 3, 7 to 11, 20 to 23, and 25 are pending. Applicants acknowledge the Examiner's comment that previous grounds of objection and/or rejection not explicitly restated and/or set forth in the present office action are withdrawn.

The Abstract has been amended to bring its total number of words within the requirements of MPEP §608.01(b). Claims 2, 3, 21 and 22 have been amended.

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In claim 2, the first occurrence of the term "4-hydroxyphenylmethyl" was deleted because it was inadvertently listed twice. In claim 3, the terms "R₃" and "R₉" were amended to teach "-C(O)-." In claims 21 and 22, the term "Pal(Me)" was corrected to read as "PalMe(3)."

Claims 4, 5 and 6 have been cancelled because the subject matter they recited has been incorporated into claim 3 as a result of the amendment to claim 3.

Claim 24 is cancelled because it is directed to non-elected claim 1.

Claim 26 is cancelled because it is directed to non-elected claim 12.

All of the aforementioned amendments are supported in the specification, as will be discussed below. Hence the amendments do not constitute new subject matter. A marked-up version of the abstract, and claims 2, 3, 21 and 22 are provided in Appendix A.

Objection to Specification

The Office action objected to the abstract because its length was not within the 150 word limit stated in MPEP §608.01(b). The abstract has been amended to bring the abstract within the limit specified in the MPEP. Specifically, the number

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of words in the abstract has been reduced, so that the abstract consists of a total 107 words.

An objection was made regarding the use of the term "organic." It was required that the term "chemical" be substituted in its place. The sentence in which "organic" appeared, has been deleted per the amendment to the abstract, and therefore this objection is no longer applicable.

Applicants note that the aforementioned objection required the deletion of text from the abstract in order to bring the total number of words within the requirements of MPEP §608.01(b). No new text was added, and therefore, Applicants submit that no new subject matter has been added. A record of the amendments to the Abstract is included in Appendix A.

Rejection Under 35 U.S.C. 112, First Paragraph

Claims 2 to 11 and 20 to 26 are rejected under 35 U.S.C. 112, first paragraph. The Office states in the present rejection and in previous communications that the specification is enabling for "Y-I-R containing compounds or closely related analogue." However, it is alleged that the specification is non-enabling under the guidelines provided in *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed Cir. 1998) for the breadth of the claimed subject matter.

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The following six factors from *Wands* were raised in support of the rejection in the office action, although *Wands* actually states eight factors.

1. The nature of the invention

Regarding claims 24 and 25, the office action states Y-I-R represents an enzymatic substrate analogue of factor Xa that has relatively high affinity for the enzyme binding. The action then concludes that "any structural variants [that] deviate from the common motif will not have selectivity on inhibiting factor Xa protease. Moreover, potency of the synthesized peptides of inhibiting Xa protease is unpredictable as to unpredictable selectivity of the produced peptides acting as specific Xa-inhibitors." Applicants respectfully traverse.

Applicants note that the premise that **any** variation from the common motif would not have selectivity on inhibiting factor Xa protease is incorrect. There is no evidence or reason to show that any variation from the Y-I-R motif would automatically result in less selectivity. Respectfully, Applicants submit that a variation from the Y-I-R motif could just as readily increase selectivity - as decrease it. Applicants submit that the only conclusion that can be drawn, is that there is likely to be some change in selectivity. Whether there is an increase or decrease can only be determined, at the current state of the technology, by experimental data. The present specification provides such data in Example XXXVI.

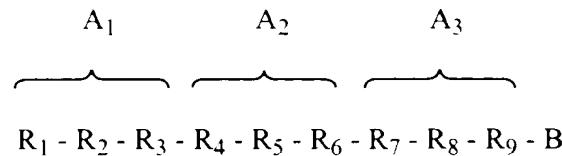
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Example XXXVI is a working example that teaches two hundred and ninety-one (291) peptide compounds that have K_i values between $100\mu M$ and $1pM$ for factor Xa inhibition. These compounds are closely related analogues of the parent compound (Y-I-R-L-P) where they are the result of multiple substitutions from the parent structure. Example XXXVI shows that despite the deviation from the Y-I-R motif, these compounds maintain factor Xa inhibition activity. Indeed some of the compounds show even greater activity. Applicants' respectfully submit that there is no objective evidence to support the proposition that variation from the Y-I-R motif necessarily results in decreased activity. And further, the specification teaches the contrary with experimental data to support the teaching.

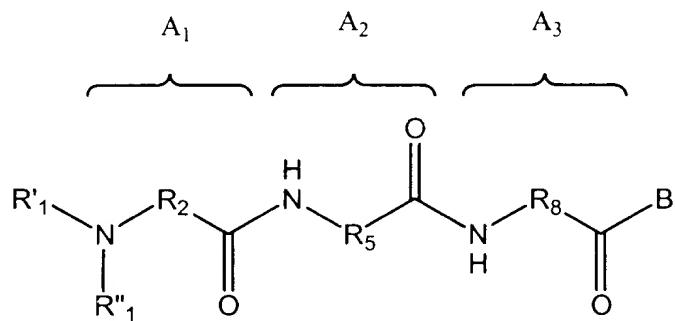
Regarding claims 2 to 11 and 20 to 23, the office action asserts that these claims do not have a common core structure. This assertion is restated a number of times in the present rejection. Applicants traverse.

Claims 2 and 3 (claim 3, as amended) are directed to peptide compounds comprising the Y-I-R motif, or closely related analogues that are three to five amino acid residues in length. The amino acids are represented by A_1 , A_2 , A_3 , and B, where B can be specifically recited one or two amino acid residues. The amino acid residues A_1 , A_2 and A_3 are further broken down according to their constituent moiety groups, R_1 , R_2 , and R_3 for A_1 ; R_4 , R_5 and R_6 for A_2 ; and R_7 , R_8 and R_9 for A_3 .

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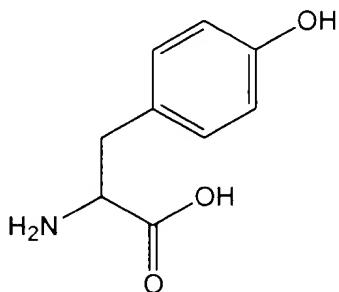
In the pending claims, R_1 , R_4 and R_7 are taught as amino moieties; R_3 , R_6 and R_9 are taught as carbonyl moieties; and R_2 , R_5 , and R_8 are taught as substituted methylene moieties. The substituent groups for the methylene moieties designates the amino acid.



For example, Y-I-R (tyrosine-isoleucine-arginine) is recited when R_2 is 4-hydroxyphenylmethyl; R_5 is 2-butyl; and R_8 is 3-guanylpropyl.

R_2 , R_5 , R_8 recites substituents that define a common core based on the Y-I-R motif. The substituents recited for R_2 , R_5 and R_8 , each have common structural, steric, and/or electronic characteristics with their respective counterparts in the Y-I-R motif. For example, R_2 recited as 4-hydroxyphenylmethyl is tyrosine,

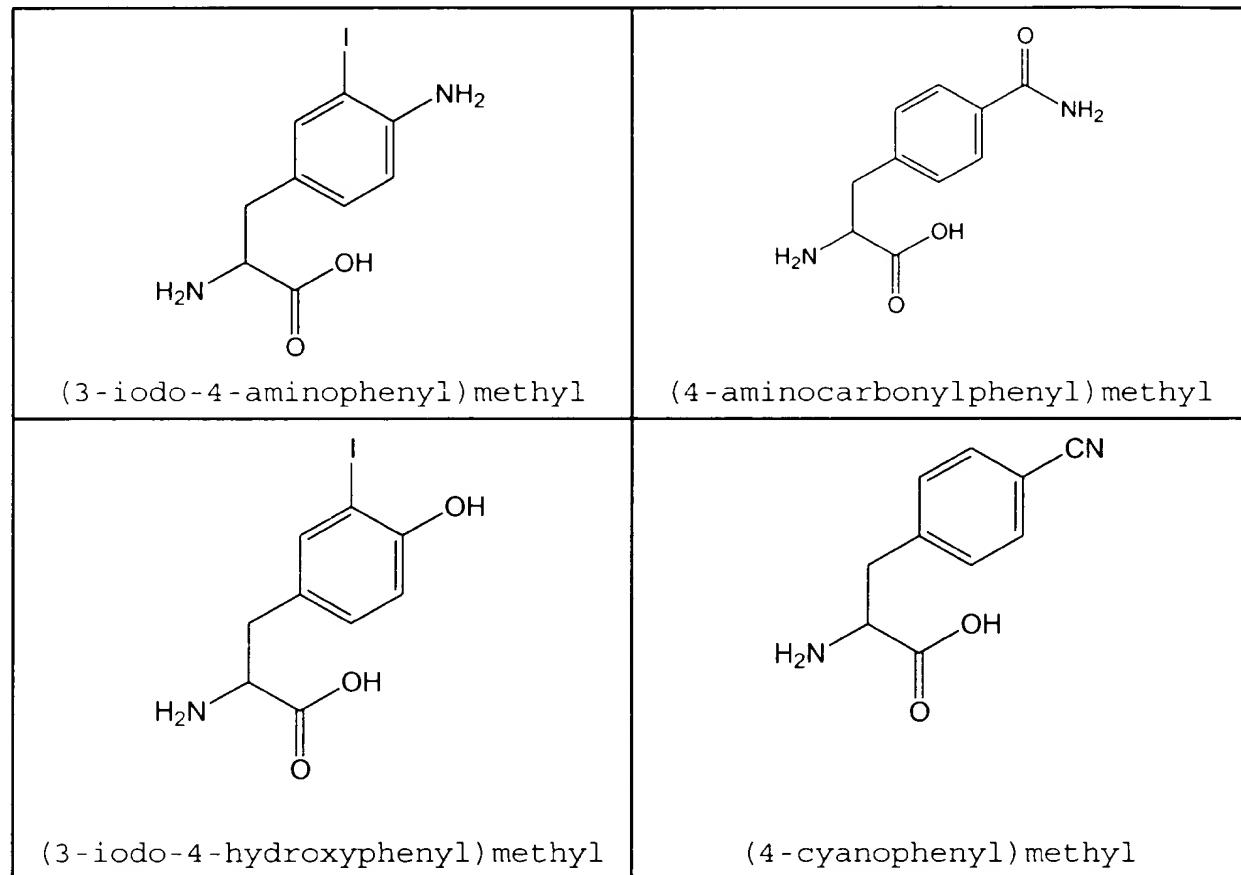
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In claim 2, R₂ recites the following moieties,

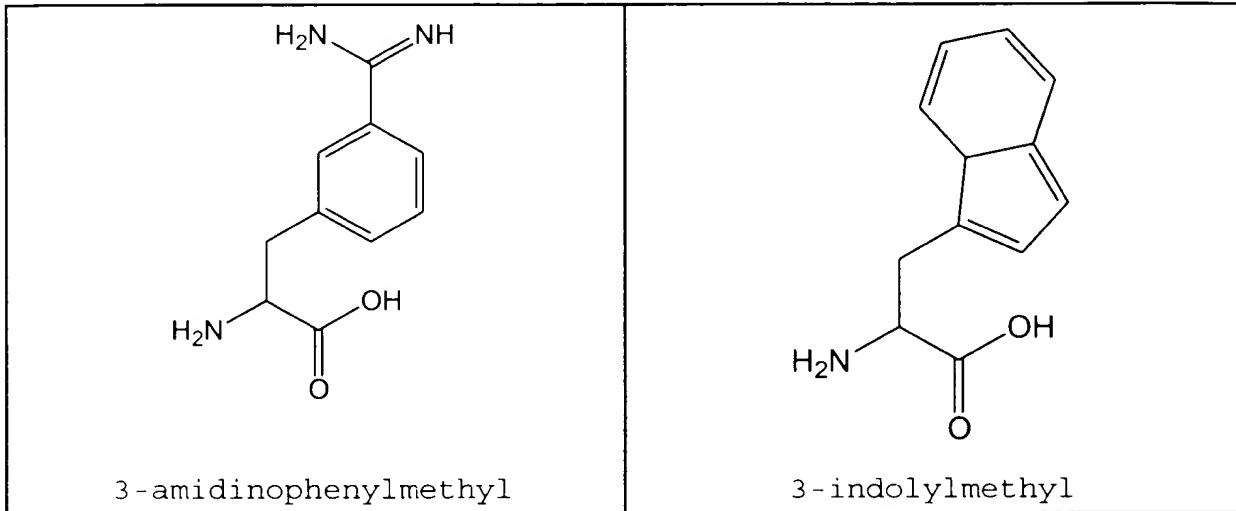
<p>4-amidinophenylmethyl ("pAph")</p>	<p>4-aminophenylmethyl ("Phe-NH₂")</p>
<p>2-naphthylmethyl</p>	<p>4 (N-methylpyridinyl)methyl</p>

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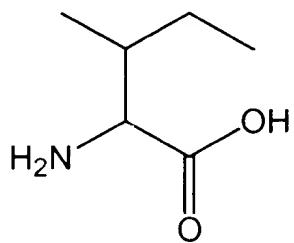
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And claim 3 recites the additional following R₂ moieties,



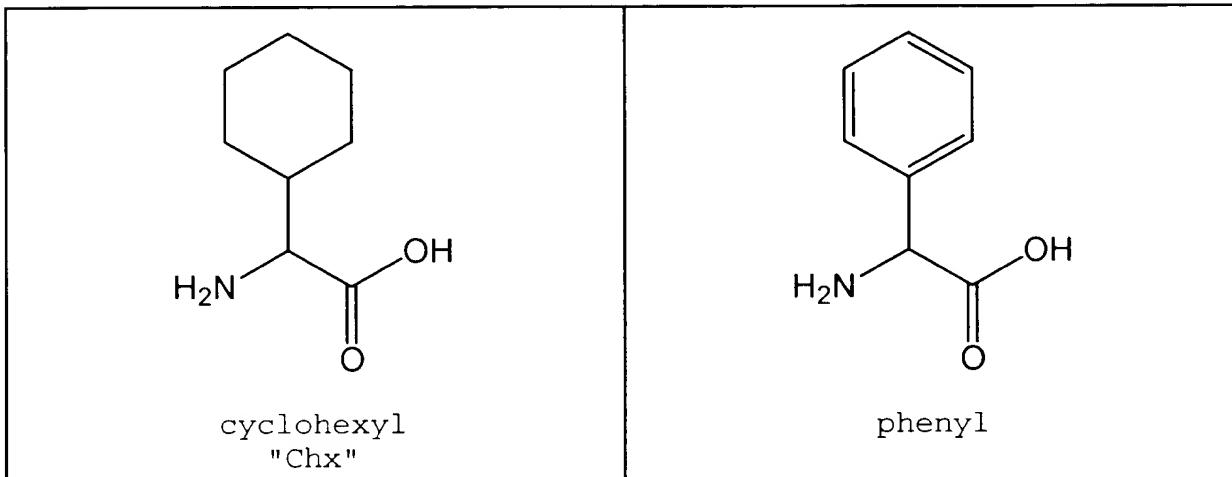
Those of ordinary skill in the art would recognize that the recited substituents possess common features, such as, the presence of an aromatic nucleus.

R₅ recited as 2-butyl is isoleucine,



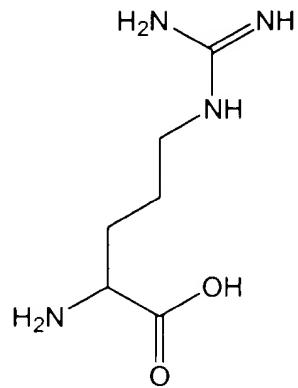
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Claims 2 and 3 also recite R₅ as the following moieties,



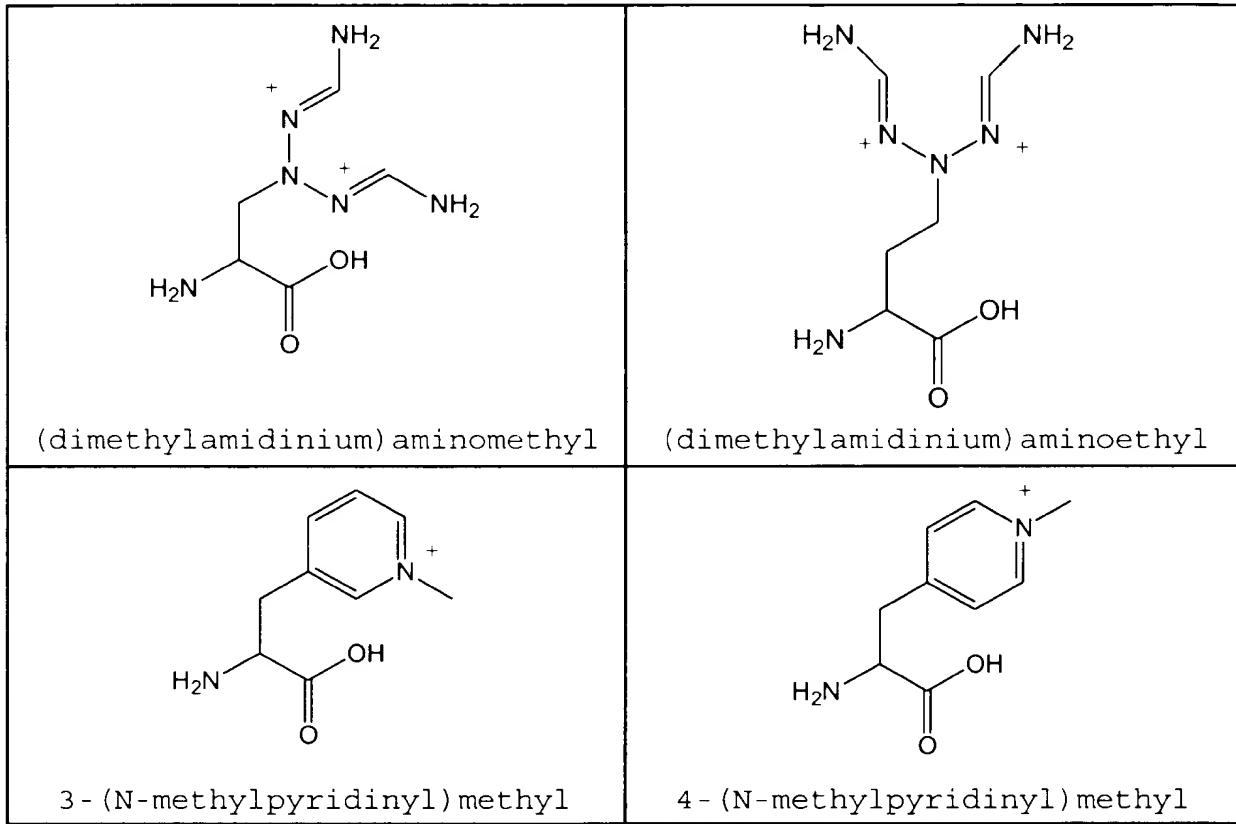
Applicants again submit that those of ordinary skill in the art would recognize a common feature of the substituents, namely, the presence of an apolar steric group.

R₈ recited as 3-guanylpropyl is arginine,

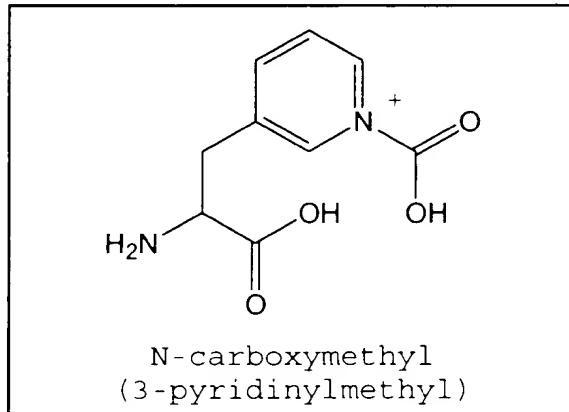


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Claim 2 also recites the following substituents for R₈



And claim 3 also recites R₈ as the following substituent,



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Those of ordinary skill in the art would recognize a common feature of the substituents, namely, the presence of a moiety with a positive charge.

2. The breadth of the claims

It is stated under this factor that the present claims do not recite a critical core structure critical to factor Xa inhibition. Applicants traverse, and refer to the discussion immediately proceeding that shows that a critical core structure is in fact recited.

3. The unpredictability

It is asserted under this factor that there is an unpredictable degree of diversity from "this core structure," and therefore the invention is unpredictable in the absence of factual indicia to the contrary. Applicants traverse, and refer to the discussion under the section "1. The nature of the Invention." Applicants note that Example XXXVI provides factual indicia that structures of the present invention with variations from the Y-I-R motif have factor Xa inhibition activity.

4. The amount of direction or guidance presented

It is asserted under this factor that the specification presents only limited guidance for Y-I-R core containing peptides and their functional assays.

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Applicants respectfully refers to their previous response (Paper No. 20, mailed October 23, 2001, pages 12 to 14) which outline in detail the breadth of the teachings of the specification. In particular, Applicants note the number of working examples (34), and the number compounds taught (485).

Applicants note that the present pending claims are strongly supported by the specification, in particular, the aforementioned working examples.

The Hofmann publication, (*Biochem. J.* (1992) Vol. 287, 943-949) is cited as showing that the substitution of a critical amino acid residue (Arg(34)) would abolish the activity of the studied protein.

Applicant submit that the Hofmann disclosure is not relevant to the present invention. First, the aforementioned substitution of a critical amino acid residue Arg(34) has no bearing to the present invention. Fig. 4 on page 947 of Hofmann shows that Arg(34) resides within a sequence that has no similarity to the Y-I-R motif of the present invention. In fact a review of Fig 4 shows that the entire protein does not contain a single Y-I-R sequence. Second, the Hofmann protein contains 119 amino acids, whereas the present invention is directed to compounds that are three to five amino acid residues in length. And lastly, the present specification provides data that demonstrates the contrary conclusion as that alleged in Hofmann. Example XXXVI refutes the conclusions drawn from Hofmann with compounds that are much more relevant to the claimed invention.

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5. The quantity of experimentation necessary

It is asserted under this factor that the specification does not provide a sufficient experimentation to enable the pending claims. Applicants traverse.

In the preceding sections and previous responses, Applicants have outlined the significant volume of experimental data taught in the specification. Applicants also note that the pending claims have been amended so that they are directed to compounds that are three to five amino acids in length. With these factors in consideration, Applicants respectfully submit that the pending claims are enabled, and can be practiced without undue experimentation.

6. The relative skill of those in the art

Applicants concur with the Examiner's conclusion that the practitioner of ordinary skill in the art would be expected to have training on a Ph.d level in fields such as, organic chemistry, biochemistry or the like.

Regarding the discussion to Hofmann in this section, Applicants respectfully submit that a practitioner of the aforementioned skill level would find the Hofmann publication as not relevant to the present invention for the reasons previously provided.

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Rejection Under 35 U.S.C. 112, Second Paragraph

Claims 2-3, 9, 11, 22, 24 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention, specifically to the following items.

Claim 2

Claim 2 is rejected as being indefinite because of improper Markush-type wording, that is, the term "and" is followed by more than one member. Regarding this rejection, Applicants have amended claim 2 so that the term "and" is followed by only one member.

Claim 2 is also rejected as being indefinite as to the term "Leu-OH." The rejection notes that the term is not defined in the specification, and queries as to whether the hydroxyl group is attached to the carboxyl terminus of leucine, or to one of the methyl moieties. The rejection indicates that this rejection also holds for claims 3, 9 and 11.

Regarding this rejection, Applicants submit that the term "Leu-OH" refers to the amino acid leucine. The term "Leu" is defined in the specification at page 12, line 29 as leucine. The term "-OH" is recognized by those of skill in the art as representing a hydroxyl group. "Leu-OH" is a notation used to indicate the presence of a hydroxyl group at the C-terminus of

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leucine. In the present case, the notation is used to emphasize that the C-terminus of the leucine is not modified beyond the carboxyl moiety, which normally contains a hydroxyl group (-OH).

This notation is commonly used by those of skill in the art to informally draw attention to a moiety in order to show that it is involved in a reaction, or otherwise modified; or as in the present case, to show that a moiety is unchanged. The emphasis was used in this particular instance, because the compound immediately preceding has a leucine where its C-terminus was amidated, that is, "Leu-NH₂." The term "Leu-OH" is used to draw the reader's attention to the moiety to show that it is different from the preceding compound.

Other instances of this notation is found in the specification. For example in Example VII, Part A (page 54, lines 4 to 12), the notation is used to emphasize the reduction of the hydroxyl group at the C-terminus of the starting material dipeptide "Fmoc-Tyr(But)-OH" to the corresponding hydride "Fmoc-Tyr(But)-H." This notation is also used similarly in Example VII, Part C to show that the starting compound, "Fmoc-Tyr(But)-{ψ(CH₂NH)}-Ile-OAllyl," which is protected at the C-terminus, is treated to obtain the de-protected product "Fmoc-Tyr(But)-{ψ(CH₂NH)}-Ile-OH."

Claim 22

Claim 22 is rejected as being indefinite because of the term "-Pal(Me)." The rejection queries as to the meaning of "Me"

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since "Me" is not defined in the specification. The rejection also notes that "PalMe(3)" is defined in the specification as β -(3-N-methylpyridinium)-alanine.

Claim 22 have been amended substituting the correct term "PalMe(3)" for the erroneous term, "Pal(Me)." Support for this amendment is found throughout the specification, for example, the preparation of the compound "Ac-D-pAph-Chg-PalMe(3)-NH₂" is taught in Example XXII (page 63).

Applicants also note that the same typographical error was made in claim 21, and hence has similarly amended this claim.

Claims 24 and 26

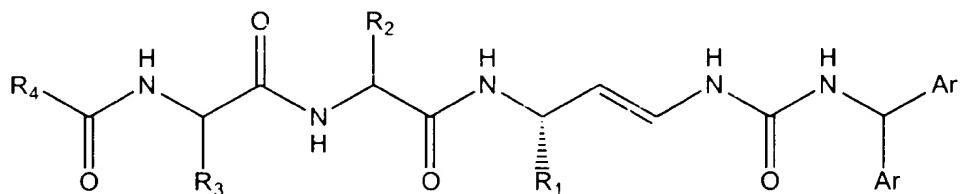
Claims 24 and 26 are rejected as being dependent on cancelled claims. Claims 24 and 26 have been cancelled.

Rejection Under 35 U.S.C. 102(e)/35 U.S.C. 103(a) - Brunck et al.

Claims 2-3 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative as obvious under 35 U.S.C. 103(a) over Brunck et al., U.S. Patent No. 5,739,112 (hereinafter "Brunck"). The rejection states that Brunck discloses compounds that read on the present invention, referencing to claims 1 to 10, and Tables 1 and 2 of Brunck. Applicants respectfully traverse.

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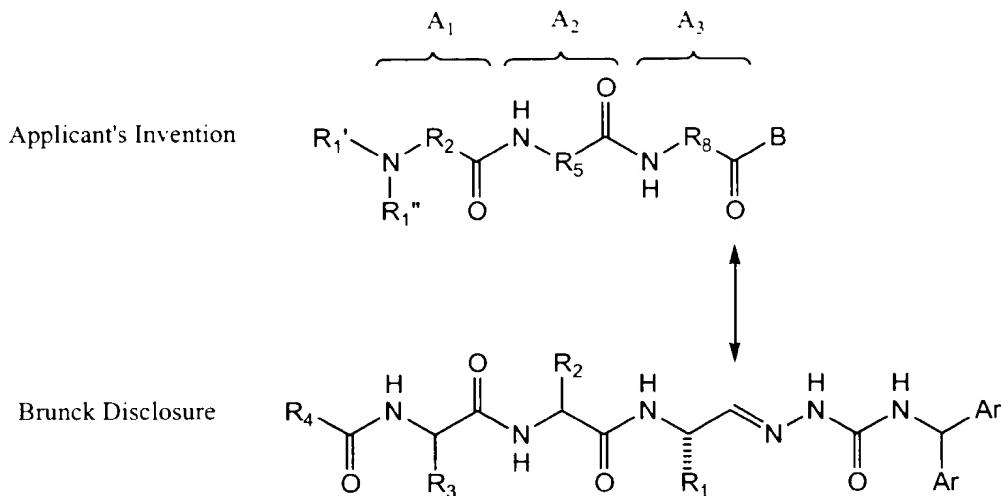
Claim 1 of Brunck provides the broadest disclosure of the compounds disclosed in the reference. Although claims 2 to 10 are independent claims, they all either directly or indirectly draw upon the structure disclosed in claim 1. Similarly, the compounds disclosed in Tables 1 and 2 of Brunck also read upon this structure, which is shown below.



Applicants' claim 2, and amended claim 3 do not read on Brunck. As noted above, claims 2 and 3 of the present invention are directed to polypeptide compounds that are at least three to five amino acids residues in length. Brunck is directed only to dipeptides.

The figure below shows the general structure disclosed in Brunck with the elements of the present invention "[R_n]" superimposed over the corresponding position in the Brunck structure.

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The double headed arrow draws emphasis to R_9 of Applicants' invention, which is " $-\text{C}(\text{O})-$," and the corresponding position in Brunck, which is a " $-\text{C}=\text{N}-$." The moieties are physically different, therefore Brunck does not anticipate the present invention. Moreover, the difference in structures results in different physical characteristics. In Brunck, the double bond is between a carbon and nitrogen atom. The double bond is also in line with the backbone of the compound, therefore the double bond's sp^2 orbital configuration prevents rotation about the bond. Conversely, in the Applicants' invention, the double bond is a carbonyl bond (" $-\text{C}(\text{O})-$ ") between a carbon and oxygen atom. A carbonyl moiety is not in line with the backbone of the compound, and it forms part of the invention's peptide backbone. Brunck clearly does not anticipate the present invention. Applicants submit that the rejection under 35 U.S.C. 102(e) should be withdrawn.

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Regarding the alternative rejection under 35 U.S.C. 103(a), Applicants' submit that there is no teaching, or suggestion in Brunck to lead one of ordinary skill to the present invention. As noted above, R, of the present invention is taught as "-C(O)-." The corresponding position in Brunck discloses "-C=N-" in place of "-C(O)-." In the present invention R, completes the peptide backbone to a tripeptide. Absent the "-C(O)-," as is the case in Brunck, there is only a dipeptide. The resultant structure in Brunck does not teach or suggest the tri- to penta- peptide backbone structure that is present in Applicants' invention.

Applicants respectfully submit that there is no teaching or suggestion in Brunck to lead one of ordinary skill to the present invention, and submit that the rejection under 35 U.S.C. 103(a) should be withdrawn.

CONCLUSION

Applicants have amended the abstract and claims 2, 3, 21, and 22. Claims 4, 5, 6, 24, and 26 have been cancelled. Therefore claims 2, 3, 7 to 11, 20 to 23, and 25 are pending. Regarding the rejection under 35 U.S.C. 112, first paragraph, Applicants traversed, and addressed the rejection by providing their position that shows the pending claims to be fully enabled. Regarding the rejection under 35 U.S.C. 112, second paragraph, Applicants have made the necessary amendments to remove the rejection. Regarding the rejection under 35 U.S.C. 102(3) or in the alternative 35 U.S.C. 103(a) citing Brunck, Applicants

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traversed, and addressed the rejection by providing arguments that show that Brunck does not anticipate, nor teach or suggest the pending claims.

In light of the Amendments and Remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he/she is invited to call Cathryn Campbell or the undersigned attorney.

Respectfully submitted,

October 2, 2002
Date

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Appendix A

FACTOR Xa INHIBITORS

ABSTRACT OF THE DISCLOSURE

The invention provides compounds which specifically inhibit factor Xa activity. ~~The compounds consist of the structure X₁-YIR X₂, wherein X₁ is H, acyl, alkyl, acylalkyl, arylalkyl or one or more amino acids, and X₂ is a modified C terminal group, one or more carboxy-protecting groups or one or more amino acids or other substituent, and Y, I and R are tyrosine, isoleucine and arginine, respectively, or peptidomimetic or organic structures that possess the same functional activity as Y, I and R, respectively. In addition, the present invention provides a compound having the structure A₁-A₂-(A₃)_m-B, where m is 0 or 1. A compound of the invention can be linear or cyclic and can be about 2 and 43 residues in length.~~

A compound of the invention is characterized, in part, in that it exhibits a specific inhibition of factor Xa activity with a K_i of $\leq 100 \mu\text{M}$, preferably $\leq 2 \text{ nM}$, and does not substantially inhibit the activity of other proteases involved in the coagulation cascade. The invention further provides methods of specifically inhibiting the activity of factor Xa and of inhibiting blood clotting *in vitro* and in an individual and methods of detecting factor Xa levels or activity.

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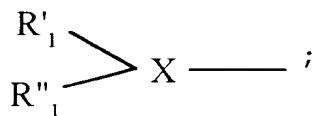
In The Claims

2. (twice amended) A non-naturally occurring compound that specifically inhibits the activity of factor Xa, having the general formula $A_1-A_2-(A_3)_m-B$, wherein m is 1;

wherein A_1 is $R_1-R_2-R_3$; A_2 is $R_4-R_5-R_6$; A_3 is $R_7-R_8-R_9$;

wherein

R_1 is



X is N ;

R'_1 is selected from the group consisting of isobutyl, 2-methylpentyl, cyclohexylmethyl, cyclohexenylmethyl, 2-methylbutyl, -H and 2,3-dimethylpentyl;

R''_1 is selected from the group consisting of 2-benzofuroyl, alloc, acetyl, trifluoroacetyl, 2-quinolinoyl, 3-pyridoyl, 4-isoquinolinoyl, 5-benzylimidazoyl, 2-naphthylmethyl, 5-pyridiminoyl, benzoyl, 2-pyridoyl, tosyl, 3-quinolinoyl, 2-naphthylsulfonyl, 2-methylbenzyl, 2-furoyl, 3,4-dichlorobenzoyl, 2-thienylacetyl,

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N(5-methyl-2-thienyl), ethoxycarbonyl,
2-fluorobenzoyl, *t*-butoxycarbonyl, benzyl and 1-20
amino acids;

R_2 is $-CR_{2A}R_{2B}-$, wherein $-R_{2A}$ and $-R_{2B}$ are independently
selected from the group consisting of -H, 4-
amidinophenylmethyl, 4-aminophenylmethyl),
4-hydroxyphenylmethyl, 2-naphthylmethyl,
4-(N-methylpyridinyl)methyl,
(3-*ido*-4-aminophenyl)methyl,
(4-aminocarbonylphenyl)methyl,
(3-*ido*-4-hydroxyphenyl)methyl, and
(4-cyanophenyl)methyl, and
(4-hydroxyphenyl)methyl;

R_3 is $-C(O)-$;

R_4 is $-NH-$;

R_5 is $-CR_{5A}R_{5B}$, wherein $-R_{5A}$ and $-R_{5B}$ are independently
selected from the group consisting of -H, 2-butyl, and
cyclohexyl;

R_6 is $-C(O)-$;

R_7 is $-NH-$;

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R_8 is $-CR_{8A}R_{8B}$, wherein $-R_{8A}$ and $-R_{8B}$ are independently selected from the group consisting of -H, 3-guanylpropyl, (dimethylamidinium)aminomethyl, (dimethylamidinium)aminoethyl, 3-(N-methylpyridinyl)methyl, and 4-(N-methylpyridinyl)methyl;

R_9 is $-C(O)-$; and

B is Leu-Pro-NH₂, Leu-Hyp-NH₂, Pen(CH₂COOH)-Pro-NH₂, Cys(CH₂COOH)-Pro-NH₂, γ -carboxyglutamic acid-Pro-NH₂, (N-carboxymethyl)Gly-Pro-NH₂, (N-carboxyethyl)Gly-Pro-NH₂, (N-1,3-dicarboxypropyl)Gly-Pro-NH₂, (N-methyl)Leu-Pro-NH₂, Leu-NH₂, Leu-OH, -NH-(4-trimethylammoniumbenzyl), -NH-[4-(1-methylpyridinium)methyl], and -NH-(4-amidinobenzyl).

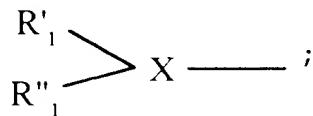
3. (twice amended) A non-naturally occurring compound that specifically inhibits the activity of factor Xa, having the general formula $A_1-A_2-(A_3)_m-B$, wherein m is 1;

wherein A_1 is $R_1-R_2-R_3$; A_2 is $R_4-R_5-R_6$; A_3 is $R_7-R_8-R_9$;

wherein

R_1 is

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X is N;

R'_1 is selected from the group consisting of H, isobutyl, 2-methylpentyl, cyclohexylmethyl, 3-quinolinyl, 2-methylbutyl, 2,3 dimethyl pentyl, and cyclohexenylmethyl;

R''_1 is selected from the group consisting of 2-benzofuroyl, alloc, acetyl, trifluoroacetyl, 2-quinolinoyl, 3-pyridoyl, 4-isoquinolinoyl, 5-benzimidazoyl, 2-naphthylmethyl, 5-pyrazinoyl, benzoyl, 2-pyridoyl, tosyl, 3-quinolinoyl, 2-naphthylsulfonyl, 2-methylbenzyl, and benzyl;

R_2 is $-\text{CR}_{2A}\text{R}_{2B}$, wherein $-\text{R}_{2A}$ and $-\text{R}_{2B}$ are independently selected from the group consisting of H, 3-amidinophenylmethyl, 4-amidinophenylmethyl, 4-aminophenylmethyl, 4-hydroxyphenylmethyl, 2-naphthylmethyl, 4-(N-methylpyridinyl)methyl, (3-iodo-4-aminophenyl)methyl, (4-aminocarbonylphenyl)methyl, (3-iodo-4-hydroxyphenyl)methyl, (4-cyanophenyl)methyl, and 3-indolylmethyl;

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R_3 is selected from the group consisting of $-C(O)-$,
 CH_2- , $CHR_{99}-C(O)-$ and $C(O)-NR_{35}-CH_2-C(O)-$,
wherein R_{35} is the CHR_{55} group of the bridging
group $-C(O)-CR_{55}-$;

R_4 is $-NH-$;

R_5 is $-CR_{5A}R_{5B}$, wherein $-R_{5A}$ and $-R_{5B}$ are independently
selected from the group consisting of $-H$, 2-butyl, cyclohexyl
and phenyl;

R_6 is $-C(O)-$;

R_7 is $-NH-$;

R_8 is $-CR_{8A}R_{8B}$, wherein $-R_{8A}$ and $-R_{8B}$ are independently
selected from the group consisting of $-H$,
3-guanylpropyl, (dimethylamidinium)aminomethyl,
(dimethylamidinium)aminoethyl,
3-(N -methylpyridinyl)methyl,
 N (carboxymethyl)(3-pyridinylmethyl), and
4-(N -methylpyridinyl)methyl;

R_9 is selected from the group consisting of $-C(O)-$,
 CH_2- and $CHR_{99}-C(O)-$; and

B is $-NH_2$, $-OH$, Leu-Pro- NH_2 , Leu-Hyp- NH_2 ,
Pen(CH_2COOH)-Pro- NH_2 , Cys(CH_2COOH)-Pro- NH_2 ,

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γ -carboxyglutamic acid-Pro-NH₂,
(N-carboxymethyl)Gly-Pro-NH₂,
(N-carboxyethyl)Gly-Pro-NH₂,
(N-1,3-dicarboxypropyl)Gly-Pro-NH₂,
(N-methyl)Leu-Pro-NH₂, Leu-NH₂, and Leu-OH.

21. (amended) A compound

Ac-D-pAph-Chg-~~Pal(Me)~~PalMe(3)-Leu-Pro-NH₂.

22. (amended) A compound

Ac-D-pAph-Chg-~~Pal(Me)~~PalMe(3)-NH₂.